

**[Patent claims]**

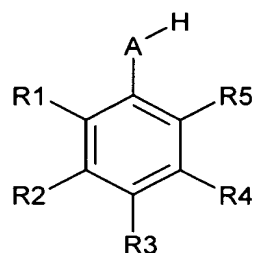
1. Method for the production of cyclic peptides, in which
  - a peptide cyclase is brought in contact with a linear peptide,
  - the linear peptide contains an acyl residue, which is activated by a nucleophilic leaving group bound chemically with this acyl residue,
  - the activated acyl residue of the linear peptide selectively acylates the center of the peptide cyclase, wherein the nucleophilic leaving group is cleaved off during formation of the cyclic peptide and
  - cyclic peptides with rings of at least 5 atoms are formed,

wherein

  - the nucleophilic leaving group, which is chemically bound to the acyl residue of the linear peptide and which activates the latter, is charge-stabilized and
  - the charge-stabilized leaving group is bound to the acyl group of the C-terminal carboxylic acid group.
2. Method for the production of cyclic peptides according to claim 1, wherein the charge-stabilized leaving groups are aromatic, heteroaromatic or araliphatic compounds, on which a hydroxy or thio group is bound to one of the ring atoms or to a carbon atom bound to the ring system.
3. Method for the production of cyclic peptides according to one of the claims 1 or 2, wherein the peptide cyclase is a NRPS or PKS cyclase, preferably a purified, isolated thioesterase domain.
4. Method for the production of cyclic peptides according to one of the claims 1 to 3, wherein the linear peptide contains proteinogenic and / or non-proteinogenic amino acids in its backbone, whereby residues which do not

derive from amino acids can also be embedded in the backbone.

5. Method for the production of cyclic peptides according to one of the claims 1 to 4, wherein the charge-stabilized leaving group is a compound of the formula



(I)

wherein applies:

A = O, S

- 10 and whereby R1, R2, R3, R4 and R5 are independent of one another:

-NO<sub>2</sub>, -CN, -F, -Cl, -Br, -I, -CH<sub>2</sub>Cl, -SO<sub>3</sub>H, -H, -NH<sub>3</sub><sup>+</sup>, -NL<sub>3</sub><sup>+</sup>,  
 -C(=O)L, -C(=O)Het, -O<sup>-</sup>, -NL<sub>2</sub>, -NH<sub>2</sub>, -OL, -OH, -NHC(=O)L,  
 -OC(=O)L, -SL, -CO<sub>2</sub><sup>-</sup>, -alkyl, -alkenyl, -cycloalkyl,  
 15 -cycloalkenyl, -heteroalkyl, -heterocycloalkyl, -aryl,  
 -heteroaryl,

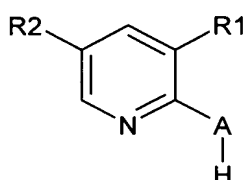
wherein

L = -alkyl, -alkenyl, -cycloalkyl, -cycloalkenyl,  
 -heteroalkyl, -heterocycloalkyl, -aryl, -heteroaryl,

- 20 wherein -alkyl stands for a group with 1 to 20 carbon atoms and -alkenyl for a monounsaturated or polyunsaturated group with 2 to 20 carbon atoms and -alkyl or -alkenyl are linear or branched; -cycloalkyl and -cycloalkenyl stand for a group with 3 to 20 carbon atoms; heteroalkyl stands for an  
 25 alkyl group wherein up to 5 carbon atoms are substituted by atoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; the heterocyclic groups stand for a residue with 1 to 20 carbon atoms wherein up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen,

oxygen, sulfur, phosphorus; aryl stands for an aromatic residue with 5 to 20 carbon atoms and heteroaryl stands for a corresponding aromatic residue in which up to 5 carbon atoms are substituted by heteroatoms chosen from the group  
 5 nitrogen, oxygen, sulfur, phosphorus.

6. Method for the production of cyclic peptides according to one of the claims 1 to 5, wherein the charge-stabilized leaving group is a compound of the formula



(II)

wherein applies:

A = O, S

and whereby R1 and R2 are independent of one another:

-NO<sub>2</sub>, -CN, -F, -Cl, -Br, -I, -CH<sub>2</sub>Cl, -SO<sub>3</sub>H, -H, -NH<sub>3</sub><sup>+</sup>, -NL<sub>3</sub><sup>+</sup>,  
 15 -C(=O)L, -C(=O)Het, -O<sup>-</sup>, -NL<sub>2</sub>, -NH<sub>2</sub>, -OL, -OH, -NHC(=O)L, -  
 OC(=O)L, -SL, -CO<sub>2</sub><sup>-</sup>, -alkyl, -alkenyl, -cycloalkyl, -  
 cycloalkenyl, -heteroalkyl, -heterocycloalkyl, -aryl,  
 -heteroaryl,

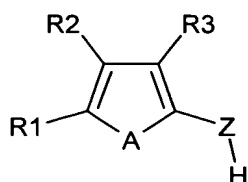
wherein

20 L = -alkyl, -alkenyl, -cycloalkyl, -cycloalkenyl,  
 -heteroalkyl, -heterocycloalkyl, -aryl, -heteroaryl,

wherein -alkyl stands for a group with 1 to 20 carbon atoms and -alkenyl for a monounsaturated or polyunsaturated group with 2 to 20 carbon atoms and -alkyl or -alkenyl are linear  
 25 or branched; -cycloalkyl and -cycloalkenyl stand for a group with 3 to 20 carbon atoms; heteroalkyl stands for an alkyl group wherein up to 5 carbon atoms are substituted by atoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; the heterocyclic groups stand for a residue  
 30 with 1 to 20 carbon atoms wherein up to 5 carbon atoms are

substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; aryl stands for an aromatic residue with 5 to 20 carbon atoms and heteroaryl stands for a corresponding aromatic residue in which up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus.

7. Method for the production of cyclic peptides according to one of the claims 1 to 6, wherein the charge-stabilized leaving group is a compound of the formula



(III)

wherein applies:

A = O, S and

15 Z = O, S,

and whereby R1, R2, and R3 are independent of one another:

-NO<sub>2</sub>, -CN, -F, -Cl, -Br, -I, -CH<sub>2</sub>Cl, -SO<sub>3</sub>H, -H, -NH<sub>3</sub><sup>+</sup>, -NL<sub>3</sub><sup>+</sup>,  
-C(=O)L, -C(=O)Het, -O<sup>-</sup>, -NL<sub>2</sub>, -NH<sub>2</sub>, -OL, -OH, -NHC(=O)L, -  
OC(=O)L, -SL, -CO<sub>2</sub><sup>-</sup>, -alkyl, -alkenyl, -cycloalkyl, -  
20 cycloalkenyl, -heteroalkyl, -heterocycloalkyl, -aryl,  
-heteroaryl,

wherein

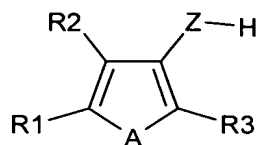
L = -alkyl, -alkenyl, -cycloalkyl, -cycloalkenyl,  
-heteroalkyl, -heterocycloalkyl, -aryl, -heteroaryl,

25 wherein -alkyl stands for a group with 1 to 20 carbon atoms  
and -alkenyl for a monounsaturated or polyunsaturated group  
with 2 to 20 carbon atoms and -alkyl or -alkenyl are linear  
or branched; -cycloalkyl and -cycloalkenyl stand for a  
group with 3 to 20 carbon atoms; heteroalkyl stands for an  
30 alkyl group wherein up to 5 carbon atoms are substituted by

atoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; the heterocyclic groups stand for a residue with 1 to 20 carbon atoms wherein up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; aryl stands for an aromatic residue with 5 to 20 carbon atoms and heteroaryl stands for a corresponding aromatic residue in which up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus.

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8. Method for the production of cyclic peptides according to one of the claims 1 to 7, wherein the charge-stabilized leaving group is a compound of the formula



(IV)

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wherein applies:

A = O, S and

Z = O, S,

and whereby R1, R2, and R3 are independent of one another:

20 -NO<sub>2</sub>, -CN, -F, -Cl, -Br, -I, -CH<sub>2</sub>Cl, -SO<sub>3</sub>H, -H, -NH<sub>3</sub><sup>+</sup>, -NL<sub>3</sub><sup>+</sup>,  
 -C(=O)L, -C(=O)Het, -O<sup>-</sup>, -NL<sub>2</sub>, -NH<sub>2</sub>, -OL, -OH, -NHC(=O)L,  
 -OC(=O)L, -SL, -CO<sub>2</sub><sup>-</sup>, -alkyl, -alkenyl, -cycloalkyl,  
 -cycloalkenyl, -heteroalkyl, -heterocycloalkyl, -aryl,  
 -heteroaryl,

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wherein L = -alkyl, -alkenyl, -cycloalkyl, -cycloalkenyl,

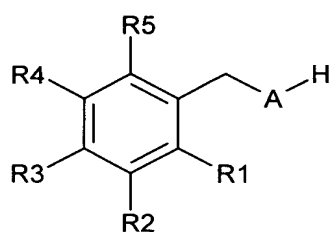
-heteroalkyl, -heterocycloalkyl, -aryl, -heteroaryl,

wherein -alkyl stands for a group with 1 to 20 carbon atoms and -alkenyl for a monounsaturated or polyunsaturated group with 2 to 20 carbon atoms and -alkyl or -alkenyl are linear or branched; -cycloalkyl and -cycloalkenyl stand for a

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group with 3 to 20 carbon atoms; heteroalkyl stands for an alkyl group wherein up to 5 carbon atoms are substituted by atoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; the heterocyclic groups stand for a residue with 1 to 20 carbon atoms wherein up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; aryl stands for an aromatic residue with 5 to 20 carbon atoms and heteroaryl stands for a corresponding aromatic residue in which up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus.

9. Method for the production of cyclic peptides according to one of the claims 1 to 8, wherein the charge-stabilized leaving group is a compound of the formula



(V)

wherein applies:

A = O, S

and whereby R1, R2, R3, R4 and R5 are independent of one another:

-NO<sub>2</sub>, -CN, -F, -Cl, -Br, -I, -CH<sub>2</sub>Cl, -SO<sub>3</sub>H, -H, -NH<sub>3</sub><sup>+</sup>,  
 -NL<sub>3</sub><sup>+</sup>, -C(=O)L, -C(=O)Het, -O<sup>-</sup>, -NL<sub>2</sub>, -NH<sub>2</sub>, -OL, -OH,  
 -NHC(=O)L, -OC(=O)L, -SL, -CO<sub>2</sub><sup>-</sup>, -alkyl, -alkenyl,  
 -cycloalkyl, -cycloalkenyl, -heteroalkyl,  
 -heterocycloalkyl, -aryl, -heteroaryl,  
 wherein  
 L = -alkyl, -alkenyl, -cycloalkyl, -cycloalkenyl,  
 -heteroalkyl, -heterocycloalkyl, -aryl, -heteroaryl,

wherein -alkyl stands for a group with 1 to 20 carbon atoms and -alkenyl for a monounsaturated or polyunsaturated group with 2 to 20 carbon atoms and -alkyl or -alkenyl are linear or branched; -cycloalkyl and -cycloalkenyl stand for a group with 3 to 20 carbon atoms; heteroalkyl stands for an alkyl group wherein up to 5 carbon atoms are substituted by atoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; the heterocyclic groups stand for a residue with 1 to 20 carbon atoms wherein up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus; aryl stands for an aromatic residue with 5 to 20 carbon atoms and heteroaryl stands for a corresponding aromatic residue in which up to 5 carbon atoms are substituted by heteroatoms chosen from the group nitrogen, oxygen, sulfur, phosphorus.

10. Method for the production of a substrate and subsequent reaction of this substrate with peptide cyclases into a cyclic peptide, wherein the substrates are linear peptides, wherein the following steps are carried out one after the other:
- Adding a reagent activating the C-terminus of the peptide acid, a coupling additive and a charge-stabilized leaving group to the free peptide acid in a solvent
  - Stirring at room temperature,
  - Addition of a base and further stirring at room temperature,
  - Filtration,
  - Removal of the solvent,
  - Deprotection of the peptide,
  - Addition of a peptide cyclase,
  - Purification of the cyclic peptide obtained.

11. Method for the production of a substrate and subsequent reaction of this substrate with peptide cyclases into a cyclic peptide according to claim 10, wherein the acyl group of the C-terminal amino acid of the linear peptide  
5 is bound to one of the leaving groups according to one of the claims 5 to 9.
12. Method for the production of a substrate and subsequent reaction of this substrate with peptide cyclases into a cyclic peptide according to claim 11, wherein the leaving  
10 group possesses a  $pK_A$  value less than or equal to 10, preferably less than or equal to 8.
13. Method for the production of a substrate and subsequent reaction of this substrate with peptide cyclases into a cyclic peptide according to one of the claims 10 to 12,  
15 wherein DCC, DCI, PyClop, HBTU, HATU, HOSu, TBTU, T3P, BopCl or 3-Cl-1-pyridinium iodide are used as an activation reagent for the free C-terminus or a side chain carboxylic acid of the peptide carboxylic acid.
14. Method for the production of a substrate and subsequent  
20 reaction of this substrate with peptide cyclases into a cyclic peptide according to one of the claims 10 to 13, wherein HOBt, HOAt or HONB are used as a coupling additive.
15. Use of cyclic peptides according to claim 1 to 14 for  
25 the production of a pharmaceutical for the therapy, diagnosis and prophylaxis of diseases in which bacterial infections occur.
16. Use of charge-stabilized leaving groups according to one of the claims 1 to 14 in a kit for the production of  
30 cyclic peptides.